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Review article

Differential diagnosis, comorbidity, and treatment of attention-deficit/hyperactivity disorder in relation to bipolar disorder or borderline personality disorder in adults

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Abstract

Background:
Attention-deficit/hyperactivity disorder (ADHD) in adults can resemble, and often co-occurs with, bipolar disorder (BD) and borderline personality disorder (BPD). This can lead to mistaken diagnoses and ineffective treatment, resulting in potentially serious adverse consequences. All three conditions can substantially impair well-being and functioning, while BD and BPD are associated with suicidality.

Objectives:
To update clinicians on the overlap and differences in the symptomatology of ADHD versus BD and BPD in adults; differential diagnosis of ADHD from BD and BPD in adults; and diagnosis and treatment of adults with comorbid ADHD-BD or ADHD-BPD.

Methods:
We searched four databases, referred to the new Diagnostic and Statistical Manual of Mental Disorders, 5th edition, used other relevant literature, and referred to our own clinical experience.

Results:
ADHD coexists in ~20% of adults with BD or BPD. BD is episodic, with periods of normal mood although not necessarily function. In patients with comorbid ADHD-BD, ADHD symptoms are apparent between BD episodes. BPD and ADHD are associated with chronic trait-like symptoms and impairments. Overlapping symptoms of BPD and ADHD include impulsivity and emotional dysregulation. Symptoms of BPD but not ADHD include frantically avoiding real/imagined abandonment, suicidal behavior, self-harm, chronic feelings of emptiness, and stress-related paranoia/severe dissociation. Consensus expert opinion recommends that BD episodes should be treated first in patients with comorbid ADHD, and these patients may need treatment in stages (e.g. mood stabilizer[s], then a stimulant/atomoxetine). Data is scarce and mixed about whether stimulants or atomoxetine exacerbate mania in comorbid ADHD-BD. BPD is primarily treated with psychotherapy. Principles of dialectical behavioral treatment for BPD may successfully treat ADHD in adults, as an adjunct to medication. No fully evidence-based pharmacotherapy exists for core BPD symptoms, although some medications may be effective for individual symptom domains, e.g. impulsivity (shared by ADHD and BPD). In our experience, treatment of ADHD should be considered when treating comorbid personality disorders.

Conclusions:
It is important to accurately diagnose ADHD, BD, and BPD to ensure correct targeting of treatments and improvements in patient outcomes. However, there is a shortage of data about treatment of adults with ADHD and comorbid BD or BPD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) persists from childhood into adulthood in around two-thirds of cases[1,2]. The persistent nature of the condition can have serious long-term consequences for individuals. In particular, adults with ADHD are more likely than the general population to suffer from educational underachievement, occupational difficulties, and low income, to engage in risky behaviors (e.g. reckless driving, dangerous sexual behavior, substance abuse, and criminality), and to suffer from mental health problems (including anxiety, depression, emotional lability, and sleep problems)[3–8].

In most cases, the diagnosis of ADHD is straightforward, based on the characteristic presentation of impairing levels of inattention, hyperactivity, and impulsivity. However, it can be difficult to diagnose ADHD in some cases, particularly when the disorder is severe and presents with mental health symptoms such as restlessness, emotional instability, low self-esteem, and sleep problems. In these cases, the symptoms and associated features of ADHD may mimic those of other mental health disorders. Most notably, bipolar disorder (BD)[8–13] and borderline personality disorder (BPD)[14,15] are characterized by symptoms that overlap with those of ADHD and can lead to inaccurate diagnosis, while depression, anxiety, and a range of other conditions (e.g. absence seizures, hypothyroidism, sleep deprivation, sleep apnea, phenylketonuria[16]) can also mimic or be mimicked by ADHD.

Making an accurate diagnosis of ADHD is further complicated by comorbidity with various conditions, including BD and BPD, since ADHD has been reported to coexist in around 20% of adult patients with BD or BPD[10,12,17–20]. This is a particular problem in general adult mental health services, where patients with BD and BPD are often referred, but where experience of the diagnosis and clinical management of ADHD is often lacking. Occasionally it can be unclear whether a patient definitely has comorbid ADHD-BD or ADHD-BPD, or whether the apparent diagnosis of one of these conditions is an artifact of overlapping symptoms[19,21]. However, in a study by Milberger *et al.*[22], in the majority of cases, the perceived comorbidity of ADHD-BD could not be explained solely by criterion overlap, and thus was likely to reflect true comorbidity of the two conditions. Nevertheless, regardless of comorbidity, failure to accurately distinguish BD, BPD, and ADHD can be extremely problematic, particularly as both BD and BPD are associated with an elevated risk of self-harm and suicide, and have unique treatment algorithms from each other and from ADHD. Furthermore, patients with ADHD who are misdiagnosed as having BD or BPD will not receive effective treatments for their ADHD, a condition associated with multiple mental health and psychosocial impairments. Patients with ADHD and comorbid BD are also likely to have a poorer prognosis relative to BD alone[23–25] and will likely require carefully tailored therapeutic regimens. While this may also be the case for BPD, there is limited data on the outcome of comorbid ADHD plus BPD.

Given the complexities of symptom overlap and comorbidity, it is not surprising that healthcare professionals with limited background training or experience in the diagnosis and clinical management of ADHD find it difficult to distinguish ADHD from other conditions such as BD and BPD. Indeed, the lack of training and experience, the lack of awareness of ADHD and its clinical presentation by both healthcare professionals and the public, and lack of continuity between child and adult psychiatric services, all contribute to explaining why ADHD is underdiagnosed or misdiagnosed in adults[4,5,26].

Accordingly, the main objectives of this review are to update healthcare practitioners on the overlap and differences in the symptomatology of ADHD versus BD and ADHD versus BPD in adults; the differential diagnosis of ADHD from BD and BPD in adults; and the diagnosis and treatment of adults with ADHD and comorbid BD or BPD. To this end, we used published literature, including diagnostic criteria from the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[27], and referred to our own clinical experiences and published consensus expert opinion, to: review diagnostic criteria for ADHD, BD, and BPD; highlight similarities and differences in symptomatology and epidemiology of ADHD versus BD and ADHD versus BPD; and provide advice for effective management and treatment of these conditions when they co-occur.

Methods

We used Ovid SP to search four databases: Embase (1974 to 22 March 2013), Medline (1946 to March Week 2 2013), Medline In-Process (to 22 March 2013), and PsycINFO (1806 to March Week 3 2013). These searches were performed using the following keywords, and their combinations and derivatives: ADHD, differential diagnosis, bipolar disorder, borderline personality disorder. The searches were limited to English language papers and, when possible, data from adults.

In total, 396 papers were identified in the four database searches. Of these, 106 publications (primary research papers, congress abstracts, reviews, and patient case studies) were selected by two reviewers (D. E.-H. and V.P.), based on whether the papers covered the following aspects:

- Symptoms of ADHD, BD, and BPD, alone and as comorbid disorders, in adults.
- Prevalence and epidemiology of ADHD, BD, and BPD, alone and as comorbid disorders, in adults.
- Treatment and management of adults with comorbid ADHD and BD or BPD.

In addition, papers not directly identified in the literature searches were included, obtained from the reference lists of papers that were identified in the searches. We also included papers that were not identified in the searches, but that we are aware of and are relevant to the topic. These papers included treatment and diagnostic guidelines, including the DSM-5, consensus guidelines on the clinical management of ADHD in adults, and research papers that reported data from children/adolescents. As the focus of this review was on adult patients, data from children/adolescents were only included if data from adults were lacking, and/or if data from children/adolescents were particularly relevant to the situation in adults. Data from children/adolescents are clearly identified as such in the review. We also refer to our own clinical experiences if published data are sparse or nonexistent.

Results

Symptoms of ADHD and comorbid BD and BPD in adults

DSM-5

Before describing the similarities and differences in symptomatology between ADHD, BD, and BPD, it is pertinent to outline how these conditions are described in the recently published DSM-5, including changes in content relative to the previous edition, DSM-IV-TR[28].

ADHD is characterized by a persistent pattern of inattention and/or hyperactivity/impulsivity that can interfere with or reduce the quality of social, academic or occupational functioning. However, when diagnosing ADHD in adults, it is important to note that the expression of key symptoms can change with age. In particular, hyperactivity and impulsiveness tend to decline with increasing age, whereas inattention tends to persist[29,30]. Symptoms such as hyperactivity may change into feelings of inner tension or restlessness[5], which can then be mistaken as signs of anxiety or depression. Furthermore, the clinical subtypes of ADHD described in DSM-IV-TR, which reflect the balance of inattentive to hyperactive/impulsive symptoms, have been shown to be developmentally unstable[5,29]; in our experience, a typical trajectory is one of hyperactive/impulsive subtype during infancy, combined subtype during childhood, and the inattentive subtype by young adulthood. In light of these findings DSM-5 has been adapted to facilitate the diagnosis of ADHD in adults and older adolescents[27]. These adaptations include:

- Descriptions of how ADHD symptoms typically present at different ages, including, for the first time in a DSM, illustrative examples of ADHD symptoms in adults. However, the 18-symptom criteria have not changed;
- Symptoms of ADHD are grouped into inattentive, hyperactivity/impulsive or combined clinical presentations, rather than the clinical subtypes;
- A reduction in the ADHD symptom threshold for adults (from the age of 17 onwards), from a requirement of $\geq$6 to $\geq$5 out of 9 items in either the inattention and hyperactivity/impulsivity domains;
- An increase in the age at which ADHD symptoms must be present, from before 7 years in DSM-IV to before 12 years in DSM-5;
- The age of onset of symptoms by age 12 no longer needs to be accompanied by impairment criteria. While impairment from the symptoms remains an essential component of the diagnosis of ADHD, it is now recognized that in some cases impairments may be compensated for by structured home and school life during childhood, with impairments emerging beyond the age of 12 years;
- DSM-5 also includes a list of associated features of the condition that support the diagnosis. This includes developmental traits such as delays in motor or social development, emotional symptoms such as frustration tolerance, irritability and mood lability, and cognitive deficits such as tests of attention, executive function and working memory.

With regard to ADHD comorbidities in DSM-5, autism spectrum disorder (ASD) is no longer a specific exclusion criterion since ASD commonly co-occurs with ADHD[27,31]. DSM-5 also states that "ADHD symptoms must not occur exclusively during the course of schizophrenia or another psychotic disorder" and "must not be better explained by another mental disorder" including BD and BPD[27]. However, studies demonstrate that ADHD, BD, and BPD are not mutually exclusive and are frequently comorbid[19,20,23,32]. Accordingly, all comorbid psychiatric conditions should be diagnosed and the patient may need treatment for more than one disorder for optimal treatment outcomes[5,11,14,16,32].

BD is an episodic condition with periods of normal mood although not necessarily a return to full function. For a diagnosis of the manic phase of BD, in DSM-5 there is now an emphasis on changes in activity and energy, in addition to changes in mood that were required in the DSM-IV-TR, to improve the accuracy of diagnosis and facilitate earlier detection[27,28]. BD can be thought of as a 'bipolar spectrum', with different classifications of BD depending on the occurrence and severity of mania and depression. In DSM-5, BD (i.e. the bipolar spectrum) is still categorized into bipolar I disorder (characterized by $\geq$1 manic episode or mixed episode of mania and depression), bipolar II disorder (no mania, but $\geq$1 hypomanic episode and $\geq$1 major depressive episode), and cyclothymia (hypomanic episodes, alternating with episodes of mild or moderate depression). The broad category of 'bipolar not otherwise

specified' is now termed 'other specified bipolar and related disorder'. Moreover, a diagnosis of bipolar I disorder no longer needs to simultaneously meet the full criteria for mania and depression in the case of a mixed episode; in DSM-5, this has been replaced with a new criterion, specifying 'mixed features' of mania or hypomania in the presence of depressive features, and of depression in the presence of manic/hypomanic features.

According to DSM-5, the main feature of BPD is "a pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity that begins by early adulthood and is present in a variety of contexts"[27]. Patients must meet five of nine criteria in the DSM-5 for a diagnosis of BPD (Table 1). The diagnostic criteria for BPD have not changed relative to DSM-IV-TR. Conversely, the layout of the manual has changed: all psychiatric disorders are listed in Section II of the DSM-5. However, an alternative method of diagnosing BPD is proposed in Section III 'Alternative DSM-5 Model for Personality Disorders', in which ≥4 of 7 pathological traits should be present (emotional lability, anxiousness, fears of rejection or separation, negative affectivity, impulsivity, risk taking and hostility), with ≥1 trait being impulsivity, risk taking or hostility.

Table 1. DSM-5 criteria for BPD, with overlapping ADHD symptoms highlighted in bold, in adults*.

DSM-5 criteria for BPD:
A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
1. frantic efforts to avoid real or imagined abandonment
2. a pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation
3. identity disturbance: markedly and persistently unstable self-image or sense of self
4. impulsivity in at least two areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating) (note: for ADHD, this does not include suicidal or self-mutilating behavior, which are covered in Criterion 5 for BPD)
5. recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior
6. affective instability due to a marked reactivity of mood (e.g. intense episode dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)
7. chronic feelings of emptiness
8. inappropriate, intense anger or difficulty controlling anger (e.g. frequent displays of temper, constant anger, recurrent physical fights)
9. transient, stress-related paranoid ideation or severe dissociative symptoms

ADHD, attention-deficit/hyperactivity disorder; BPD, borderline personality disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders.
*Based on a table from Philipsen[14]. The criteria for BPD are the same in DSM-5[27] as in DSM-IV-TR[28].

Key similarities and differences in symptomatology

Several clinical investigators assert that BD and ADHD are clinically distinguishable in adults (e.g. Scheffer[11]; Skirrow *et al.*[12]; Wilens *et al.*[25]; Torralva *et al.*[33]; Nierenberg *et al.*[34]). In particular, the time-course of symptom presentation is critical to differentiating ADHD from BD, i.e. bipolar patients present with symptoms in discrete episodes of mania/hypomania and depression (changes in activity, energy and mood from the premorbid state should be detectable)[27], whereas symptoms associated with ADHD follow a persistent trait-like course[12,25,35]. In addition, as shown in Tables 2 and 3, while ADHD has several symptoms in common with depressive and manic episodes of BD, there are also notable differences. For instance, in patients with BD, symptoms that are often apparent during manic episodes (i.e. elation, decreased need for sleep, and grandiosity) and depressive episodes (i.e. psychomotor retardation, fatigue or loss of energy, hypersomnia, loss of interest in pleasure, and thoughts of death/suicidality) are not part of the ADHD syndrome[11]. Moreover, there can be subtle differences in overlapping symptoms. For instance, patients with ADHD may present with low mood, perhaps due to frustration and poor achievement in school, work or social relationships, leading to low self-esteem and low self-confidence, but this does not necessarily reflect a comorbid depressive disorder[11]. Another subtle difference can be found in the flow of thoughts. Adult patients with ADHD typically experience a distracted type of ceaseless mental activity and wandering mind (everyday thoughts flitting from one topic to another), whereas in BD

Table 2. Diagnostic symptoms of bipolar mania from DSM-5 and relatedness of ADHD symptoms*.

Symptoms of mania in BD	Symptoms of ADHD†	Degree of overlap
Distractibility	Easily distracted	Extensive
Irritability	Irritability‡	Extensive
More talkative	Talks excessively$	Moderate
Psychomotor agitation	Hyperactivity	Moderate
Elation		Little
Grandiosity		Little
Flight of ideas/racing thoughts		Little
Decreased need for sleep	Difficulty settling for sleep	Little
Increased goal-directed activity		Little
Excessive involvement in activities that have a high potential for painful consequences		Little

ADHD, attention-deficit/hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; BD, bipolar disorder.
*Based on a table from Scheffer[11], updated according to DSM-5[27].
†ADHD symptoms are trait-like, starting in childhood, whereas BD symptoms reflect a distinct change from the premorbid state.
‡Not part of the definition of ADHD.
$Overactivity in ADHD is often under partial control, i.e. patients can be calm and focused some of the time, depending on what they are doing.

Table 3. Diagnostic symptoms of bipolar depression from DSM-5 and relatedness of ADHD symptoms*.

Symptoms of depression in BD	Symptoms of ADHD†	Degree of overlap
Insomnia	Difficulty settling‡	Extensive
Irritability	Irritability‡	Extensive
Difficulty concentrating	Inattention	Extensive
Psychomotor agitation	Hyperactivity	Moderate
Fatigue or loss of energy	Fatigue or loss of energy‡ can be linked to inattention in ADHD	Moderate
Depressed mood	Low self-esteem‡	Little to moderate
Weight loss/gain		Little
Psychomotor retardation		Little
Hypersomnia		Little
Loss of interest in pleasure		Little
Thoughts of death/ suicidality		Little

ADHD, attention-deficit/hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; BD, bipolar disorder.
*Based on a table from Scheffer[11], updated according to DSM-5[27].
†ADHD symptoms are trait-like, starting in childhood, whereas BD symptoms reflect a distinct change from the premorbid state.
‡Not part of the definition of ADHD.

thoughts may be 'racing' and may be perceived as particularly sharp or 'on the ball'[36].

Several features of BPD overlap with those of ADHD, including symptoms emerging out of childhood, a chronic trait-like course, emotional instability[37,38], impulsivity[14,39,40], and risk taking behavior, particularly in males[14,41,42]. Deficits in affect regulation, such as emotional instability, are a key feature of BPD but are also recognized as an associated feature of ADHD[38]; the presence of mood instability supports the diagnosis of ADHD[27], but does not define the condition due to the lack of specificity to the condition. Adults with ADHD may also show disturbed interpersonal relationships as a consequence of ADHD symptoms, akin to disturbed relationships experienced by patients with BPD[14]. Patients with BPD may experience a special form of inattention as part of dissociative states when they feel emotionally stressed, particularly in response to feelings of rejection, failure, and being alone. In contrast, the attention deficits seen in ADHD are particularly prominent in situations that lack external stimulation (e.g. during boring, routine or familiar tasks)[14]. Another feature of BPD is a tendency to resort to self-injurious behavior in order to alleviate tension, whereas self-injurious behavior per se is not a feature of ADHD; while patients with ADHD are more likely to regulate emotional symptoms through extreme sports, novelty seeking, sexual activity, and aggression[14]. Diagnostic criteria for BPD, with similarities to diagnostic criteria for ADHD highlighted, are shown in Table 1.

In addition to the symptom profile at the time of assessment, ADHD may also be differentiated from other diagnoses by the age of onset. While DSM-5 states that 'several' ADHD symptoms should be present before the age of 12 years, in most cases the full syndrome (i.e. six or more symptoms of either inattention or hyperactivity/impulsivity, associated with impairment) is present during childhood[6]. This is the most characteristic presentation of ADHD in adults, as a childhood disorder that persists into adulthood. In contrast, the first symptoms of BD usually become apparent later in life, often during late adolescence and early adulthood[43]. With regard to BPD, emerging symptoms of the disorder typically present during adolescence or early adulthood; however, signs of the disorder may also be observed in childhood in some cases[44]. For these reasons, ADHD and BPD are difficult to distinguish on the basis of childhood or adolescent onset, in addition to the chronic trait-like course that is common to both disorders. Summaries of the key differences between ADHD versus BD, and of the key similarities and differences between ADHD and BPD, are shown in Tables 4 and 5, respectively.

Table 4. Summary of key differences between ADHD and BD*.

ADHD	BD
Childhood or early adolescent onset	Adolescent/adult onset
Trait-like, no change from premorbid state	Episodic course, change from premorbid state
May be excitable, but not grandiose/elated	Grandiosity/elated
Reports being unable to function	Reports high level function, not reflecting behavior
Chronic low self-esteem	Episodes of depression
Usually possesses insight	Tends to lack of insight
Difficulty getting off to sleep	Reduced need for sleep
Complains of being unable to concentrate/focus	Subjective sense of sharpened mental abilities
Restless (fidgety, difficult being still)	Marked overactivity and agitation

ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder.
*Constructed using criteria from Kooij *et al.*[6] and DSM-5[27].

Screening

It is possible to screen for ADHD, BD and/or BPD, to tentatively identify patients who may be affected by one or more of these conditions, prior to further detailed diagnostic assessments. However, while these screening tools have been evaluated for their accuracy in identifying cases of the primary conditions against healthy controls, there is limited data on their ability to distinguish between the three conditions, or to identify comorbid cases. Screening tools should never be used to establish the diagnosis, but may be used to obtain baseline measures to identify potential cases and for monitoring the effectiveness of treatment.

ADHD screening in adults can be done in as little as 3–5 minutes per patient[47]. Kooij[48] has suggested four

Table 5. Summary of key similarities and differences between ADHD and BPD*.

ADHD	BPD
Childhood onset or early adolescent onset	Early adult/adolescent onset; signs in childhood in some cases
Defined by impairment	Defined by impairment
Chronic-like trait	Chronic-like trait
Pervasive across situations	Pervasive across situations
Affective lability	Affective lability
Impulsive	Impulsive
Inattention	Inattention is not a core feature; frantic efforts to avoid real or imagined abandonment
	Recurrent suicidal behavior

ADHD, attention-deficit/hyperactivity disorder; BPD, borderline personality disorder.
*Constructed using criteria from Kooij *et al.*[6], DSM-5[27], Linehan[44], Miller *et al.*[45], and Distel *et al.*[46]

yes/no questions to screen for ADHD in adults. Alternatively, the Adult ADHD Self-Report Scale (ASRS) can be used to screen for symptoms of ADHD that are present in adulthood. The specificity of the ASRS may be improved when used in conjunction with a scale for childhood symptoms of ADHD, such as the Wender Utah Rating Scale (WURS), to identify whether symptoms of ADHD were present during childhood[49,50]. In the UK we advise use of current and retrospective 18 item DSM checklists, which provide a comprehensive screen for the core symptoms that define the disorder[51,52]. These screening tools are thought to have high sensitivity, but may lack specificity, particularly in comorbid populations[53]. Other potential screening tools include tests of cognitive function, such as A Quick Test of Cognitive Speed (AQT) (sensitivity 93%, specificity 100%)[54] and Quantified behavior Test (QbTest) (sensitivity 68%, specificity 65%)[55,56]; however, the sensitivity and specificity of these tests have yet to be shown to be sufficiently robust in large enough patient populations, and may not discriminate well enough from comorbid conditions, for them to be applied in routine clinical practice.

BD can be screened using several rating scales, such as the Hypomania Checklist (sensitivity 80%, specificity 51%, for BD versus major depressive disorder)[57], the Mood Disorder Questionnaire[58], and the 19-item Bipolar Spectrum Diagnostic Scale (BSDS)[59], although screening tools for BD may have low sensitivity and limited diagnostic validity[59]. Moreover, when screening for BD, we must distinguish between patients who are experiencing an active episode of hypomania/mania or depression from those who are in between episodes, when symptom scores are likely to be low. For example, we recently found that women with ADHD gave higher scores on bipolar symptom rating scales, than euthymic women with bipolar I disorder in between episodes[60].

For BPD, Zanarini *et al.*[61] developed a test (sensitivity 81%, specificity 85%) that enables adults to be screened very briefly, and with acceptable psychometric performance; the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD) consists of 10 self-reported items that are based on DSM-IV diagnostic criteria.

ADHD, bipolar I disorder, major depressive episode, and generalized anxiety disorder (GAD) can also be simultaneously screened using the Provisional Diagnostic Instrument (PDI-4), a brief, 17 item, self-rating tool[62]. Using PDI-4, screening for BD is based on current or past occurrence of symptoms of mania. When PDI-4 was tested in 1047 adults, sensitivities were moderate (ranging from 52% for mania to 70% for ADHD), and specificities were strong (ranging from 86% for mania to 92% for GAD)[63]. However, the authors concluded that "the high level of symptom overlap between these diagnoses emphasizes that such brief scales are not a replacement for thorough diagnostic evaluation by trained medical providers"[63]. Indeed, screening tools should never be used as substitutes for comprehensive diagnostic interviews.

Diagnosis

To diagnose ADHD in adults, we recommend that clinicians use the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) or the structured Diagnostic Interview for ADHD in adults (DIVA 2.0)[64,65]. Both interviews provide a systematic evaluation of the DSM-IV criteria for ADHD. CAADID has been widely used in research and validated against rating scale, clinical outcome and treatment data. The DIVA, developed by a European group, has been translated into multiple languages by members of the European Network Adult ADHD. Unlike CAADID, DIVA 2.0 is available free of charge at www.divacenter.eu[65], and DIVA 2.0 also provides a wider range of examples for each ADHD symptom than CAADID, in addition to a comprehensive section on the impairments linked to the symptoms of the disorder.

When diagnosing ADHD, a complete cluster of symptoms is needed, as specified in the DSM-5, i.e. $\geq$5 out of 9 items in either the inattention and/or hyperactivity/impulsivity domains in adults, and $\geq$6 out of 9 items in childhood[27]. When the full symptom cluster(s) can be clearly identified during childhood, and if this follows a trait-like course into adulthood, it is rarely difficult to distinguish ADHD from other conditions. This is because it is unusual for any other conditions to generate the entire symptom cluster and typical developmental course that defines ADHD. While some symptoms such as poor concentration and distractibility may arise in many other conditions, the full cluster of ADHD symptoms is much less likely to arise. As a consequence, a good developmental account of the

onset and course of the ADHD symptoms that define inattention and hyperactivity/impulsivity is usually sufficient to delineate ADHD from other conditions.

However, establishing the diagnosis of ADHD can sometimes be complicated by symptoms of ADHD that are masked by the patient's learned compensatory mechanisms[66]. This may be particularly true for symptoms of self-organization, planning, and forgetfulness, where simple strategies to manage these problems can be implemented. In these cases, associated features of ADHD (e.g. emotional instability, being easily frustrated or overwhelmed and behavioral problems arising from longstanding impairments) could lead to a presentation that overlaps with that of BPD. Compensatory mechanisms that patients may use to mask their ADHD symptoms include choice of career, use of an electronic organizer such as a smartphone, and other people 'covering' for them[66]. However, if these compensatory mechanisms are particularly successful, then this may indicate that the individual does not have ADHD or has only mild impairments that do not need treatment[67]. Moreover, self-awareness of ADHD symptoms is difficult for some adult patients, because they have lived with their symptoms since childhood[47,68]. Thus, when assessing an adult patient for ADHD, it is often helpful to interview or obtain information from family, friends, coworkers, or school records[48].

Depression and mania can be rated in BD using the Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS), respectively[33,69,70]. With regard to differentiating ADHD from BD, one small-scale study of 15 patients with BD, 16 patients with ADHD, and 15 healthy controls by Torralva *et al.*[33] suggests that it may be possible to differentiate ADHD from BD based on a neuropsychological test battery. In particular, Torralva *et al.*[33] found that patients with ADHD performed significantly better than patients with BD on the recognition phase of both the Rey list memory task ($p = 0.024$) and the Rey Figure ($p = 0.027$), possibly reflecting the crucial role of the executive component on memory deficits in patients with ADHD, relative to BD. Also, relative to controls, patients with BD performed worse ($p < 0.05$) on immediate verbal memory tasks, and patients with BD and patients with ADHD both had lower scores in the recognition phase of verbal and non-verbal memory tasks, and in a task of executive functioning with high working memory demand[33]. However, these conclusions represent preliminary findings and are not sufficiently robust to guide clinical practice. As such, clinical interview remains the only valid method to distinguish between the disorders at the current time.

The Revised Diagnostic Interview for Borderlines (DIB-R) is the most widely accepted measure of BPD[71]. Alternatively, the following structured interviews are also available to diagnose personality disorders: the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II)[72], the International Personality Disorder Examination (IPDE)[73], the Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV)[74], and the Structured Interview for DSM-IV Personality (SIDP-IV)[75]. In addition, a variety of other scales have been developed to assess severity and change in persons with BPD, including the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD)[76]. The importance of assessing the severity of BPD (in addition to diagnostic occurrence) is increasingly recognized as it has an important bearing on treatment outcome[77].

Prevalence and epidemiology of ADHD, BD, and BPD

ADHD, BD, and personality disorders are common in clinical practice. ADHD has been found in 17–22% of psychiatric outpatients who were having clinical consultations for reasons other than ADHD[50,78,79] while, in another study, 45.5% of outpatients had personality disorders, of which BPD was one of the most common[80].

ADHD, BD and BPD as individual disorders

In general population surveys, ADHD has been estimated to affect 2.5 to 4.4% of adults[81–83]. Notably, in one large survey ($n = 11,422$) in the Americas, Europe and the Middle East, higher proportions of adults were reported to have ADHD in higher income countries (4.2% overall, including 5.2% in the US and 7.3% in France) than in lower income countries (1.9% overall, including 1.8% in Lebanon and 1.9% in Columbia)[82]. In children, ADHD appears to be more prevalent in boys than girls (estimated ratios range between 2:1 and 9:1). However, it is unclear whether ADHD is more common in men than in women, or vice versa[50,78,79,84,85]. A large epidemiological survey ($n = 15,198$) in twins showed higher levels of inattentive symptoms in adult males than females, but similar levels of hyperactive/impulsive symptoms[85]. Conversely, in a study by Almeida Montes *et al.*[79], a higher proportion of women (21.6%) than men (8.5%) who attended psychiatric clinics as outpatients ($n = 161$) were diagnosed with ADHD; interestingly these patients often attended for conditions other than ADHD, i.e. mainly depressive and anxiety disorders that are more common in women than men[79]. These results do not necessarily mean that a higher proportion of women than men have ADHD, but they may indicate a higher mental health burden for women with ADHD compared to men with ADHD. In a study of 3529 patients who attended GPs' surgeries, Bitter *et al.*[86] estimated that the prevalence of ADHD was higher in men (~3.5%) than in women (~1.1%) age ≤40 years, but similar (<1%) in men and women >40 years. However, as in Almeida Montes *et al.*[79], it is also uncertain whether the

data reported by Bitter *et al.*[86] could have been biased by any confounding factors (e.g. comorbidities), as reasons for each patient's attendance in GPs' surgeries were not disclosed.

The prevalence of BD has been estimated in the "World Health Organization (WHO) World Mental Health survey (WMH) initiative", a survey of 61,392 adults in the general populations of 11 countries in North and South America, Asia, Oceania, and Eastern Europe. Lifetime prevalence of BD-I was 0.6%, BD-II was 0.4%, and bipolar spectrum was 2.4%. Twelve-month prevalence of BD-I was 0.4%, BD-II was 0.3%, and BDS was 1.5%[87]. The prevalence of BD appeared to differ by country (e.g. the lifetime prevalence of bipolar spectrum ranged from 4.4% in the USA to 0.1% in India)[87], although, in a review of several other population surveys by Ayuso-Mateos[88], available on the WHO website, BD had similar prevalence in different regions of the world, including Europe, North America, Oceania, Africa, and South Asia. Similarly, in the review by Ayuso-Mateos[88], BD appears to affect equal proportions of men and women when comparing results from 12 population surveys from around the world, e.g. the lifetime prevalence of BD was 1.6% for males and 1.7% for females in the USA and 1.6% for males and 1.6% for females in Taiwan.

BPD prevalence is around 1% in adults, based on community surveys in America and Europe, including Great Britain ($n = 626$) by Coid *et al.*[89] and Baltimore, US ($n = 742$) by Samuels *et al.*[90]. Grant *et al.*[91] reported a lifetime prevalence of 5.9% for BPD in lay persons' interviews of 34,653 adults in the US. However, differences in prevalence between the Grant *et al.*[91] study and those reported by Coid *et al.*[89] and Samuels *et al.*[90] are likely to reflect variation in methods of case detection used in these studies. In addition, there is no convincing epidemiological evidence that BPD is more common among women than men. Indeed, Grant *et al.*[91] could not find any statistically significant difference between the lifetime prevalence of BPD in men (5.6%) and women (6.2%), with an odds ratio (99% confidence interval) of 1.0 (0.83–1.12), and a larger proportion of men (1.0%; 9 patients) than women (0.4%; 7 patients) had BPD in the aforementioned British survey by Coid *et al.*[89].

Naturally, prevalence data are heavily influenced by diagnostic criteria and associated cut-points. The changes to DSM-5 may lead to an increase in the population prevalence of ADHD in adults, relative to the DSM-IV-TR criteria. Furthermore, the diagnostic criteria for BD in DSM-IV and DSM-5 are reliable but not necessarily valid. Studies which have applied different sets of diagnostic criteria to large numbers of cases include the Bridge Study[92]. In this large, international study many cases of BD were captured using a less stringent set of diagnostic criteria. Contrary to some expectations, these broader definitions were no less valid (based on the following validators: history of mania/hypomania among first degree relatives, two or more lifetime episodes and first symptoms having occurred before age 30) but importantly had higher rates of psychiatric comorbidity[93]. Also, in the National Comorbidity Survey Replication, a survey of 9282 adults in the general population of the US, a high prevalence of BD (9% of participants) was reported when BD was broadly defined by the co-occurrence of depression with mania, hypomania or subthreshold hypomania[94]. Thus the threshold of diagnostic criteria for bipolar disorders is an important consideration when reviewing comorbidities.

ADHD and BD comorbidity

Adults are frequently diagnosed with concomitant ADHD and BD: 5–20% of adults with ADHD may also have BD[10,12,17,18], although Halmøy *et al.*[58] did report a higher rate (32%), and 10–21% of adults with BD may have comorbid ADHD[10,18,23,34]. However, because of similarities between symptom profiles, particularly if the developmental courses of the different disorders are not taken into account, pure ADHD or pure BD may be mistaken for comorbid ADHD-BD (and vice versa). Depending on the methodology applied, this will naturally affect estimates of ADHD-BD comorbidity prevalence rate estimates[8,12]. For example, it is a particular concern that the emotional instability which is commonly seen to accompany ADHD should not be mistaken for BD, as this may lead to misleadingly high ADHD-BD comorbidity prevalence rates if screening/diagnostic rating scales are used that do not discriminate well between the two conditions[12].

It is suggested that adults with concomitant ADHD and BD may experience exacerbated symptoms and outcomes, relative to each condition alone[23–25]. For example, it has been suggested that this includes experiencing mania symptoms an average of 3–5 years earlier than BD-only patients[34,95], having more frequent affective episodes, particularly depression[96,97], more severe affective symptoms, shorter duration of wellness, lower educational achievement, fewer relationships, more suicide attempts and more legal problems[8,24,34].

With regard to the high rate of comorbid ADHD with BD, Sachs *et al.*[98] suggested that this may be explained by four hypotheses:

(1) Comorbidity occurs by chance.
(2) Comorbidity may be an artifact of overlapping symptomatology.
(3) Comorbidity is based on a predisposed susceptibility to contracting separate illnesses.
(4) Symptoms of ADHD before the onset of BD may be prepubescent illness prior to a full affective episode.

Skirrow and colleagues[12] reviewed the available literature on the high rate of comorbid ADHD with BD, and

concluded that comorbidity could not occur by chance because rates were higher than predicted according to the prevalence of the individual disorders. Although, as discussed above, it is hard to exclude an inflation of estimated comorbidity rates from the application of criteria that do not clearly distinguish between the two disorders. Review of follow-up studies also failed to identify a risk of ADHD being a developmental precursor of BD, although there are as yet insufficient long-term follow-up studies to exclude this possibility. Overall, the current data are most consistent with the view that there is increased comorbidity and that the high co-occurrence rates are due to shared etiological (most likely genetic) risk factors[99].

Other practitioners suggest that ADHD-BD comorbidity may be a distinct clinical phenotype of BD in children[95,100,101]; Faraone *et al.*[100,101] based this conclusion on familial comparisons. Moreover, neuroanatomical differences in adults with ADHD, BD and ADHD-BD support this hypothesis[102–105]. However, shared liability is difficult to exclude, and several of these studies do not focus on traditional BD but on a severe form of emotional self-regulation.

ADHD and BPD comorbidity

In two studies, 16.1% and 38.1% of adults with BPD had comorbid ADHD[19,20]. Ferrer *et al.*[20] found that adult patients with BPD could be categorized into two subgroups, based on ADHD comorbidity: patients with comorbid ADHD-BPD had a more homogeneous and impulsive profile, while patients with BPD without ADHD were more likely to have anxiety and depressive disorders. Avoidant personality disorder only affected patients with BPD without ADHD[20]. It may also be the case that adults with the combined type presentation of ADHD are more likely to have BPD than those with predominantly inattentive presentations of ADHD[106], perhaps due to the overall severity of the disorder when the combined presentation of ADHD persists into adulthood. Thus this study suggests that BPD is most often seen in adults with the most severe and persistent forms of ADHD, when both symptom domains persist. Furthermore, emotional instability, a core component of BPD, is strongly linked to the hyperactive/impulsive symptoms of ADHD and therefore more likely to be prominent in patients where significant hyperactivity/impulsivity persists into adulthood[107,108].

For ADHD and BPD, neuroimaging studies suggest that there may be some shared neurobiological dysfunction, thus a degree of overlap may exist in underlying brain dysfunctions, as well as in symptomatology. For instance, there may be dysfunctions of the prefrontal cortex, a core region for attentional mechanisms and impulse control, and in the orbitofrontal cortex, a core region for impulsivity and emotional control[109–113].

Management of patients with comorbid ADHD and BD or BPD in clinical practice

Given that the symptoms of ADHD overlap with BD, BPD and other disorders (e.g. absence seizures, hypothyroidism, sleep deprivation, sleep apnea, phenylketonuria)[16], it is essential to obtain accurate diagnoses, as different disorders and comorbidities necessitate the use of different therapeutic regimens. In relation to the management of adults with comorbid ADHD-BD or ADHD-BPD, our key clinical recommendations are summarized in Figures 1 and 2. These recommendations and associated literature are discussed in more detail below.

Taking into account that ADHD is underdiagnosed in adults, Klassen *et al.*[8] stated that it is likely that BD alone tends to be treated in adults presenting with symptoms of both ADHD and BD. Use of BD medications alone in patients who also have ADHD may not always be problematic, as it is possible that some neurobiological pathways may be common to ADHD and BD (e.g. dopaminergic, noradrenergic and serotonergic systems)[8]. Thus, BD medications may improve some ADHD symptoms[8], although we are not aware of any direct evidence

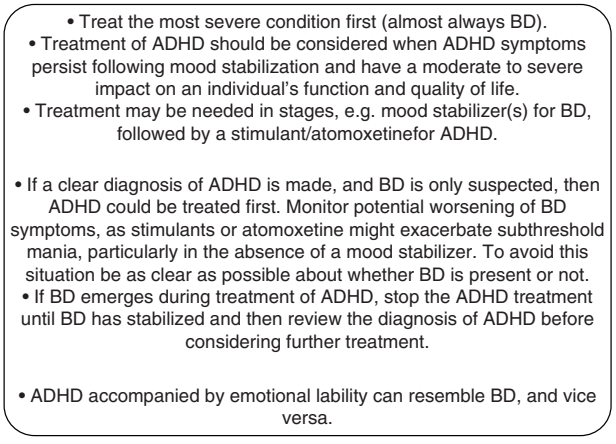

Figure 1. Management of comorbid ADHD-BD in adults: our key clinical recommendations. ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder.

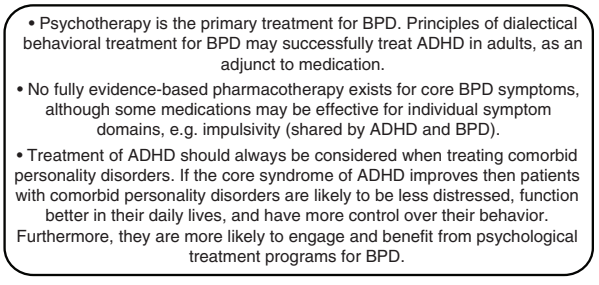

Figure 2. Management of comorbid ADHD-BPD in adults: our key clinical recommendations. ADHD, attention-deficit/hyperactivity disorder; BPD, borderline personality disorder.

for this. Similarly, Klassen *et al.*[8] also contended that when BD symptoms are more severe than those of ADHD (which is nearly always the case) treatment of BD alone may yield adequate outcomes, with relatively low levels of residual impairments if the ADHD is not too severe. In our clinical experience, patients with ADHD-BD should be treated for BD first, and residual levels of symptoms/impairments arising from ADHD should then be assessed; most notably, those patients with ADHD-BD that remain highly dysfunctional in between episodes of mania and depression, presenting with the core symptoms of ADHD, should be treated for these symptoms whenever possible. Moreover, treatment of BD alone in patients with comorbid ADHD may result in residual symptoms that could be due to ADHD even if the patient is subthreshold to the diagnostic criteria for ADHD after BD treatment. These residual ADHD symptoms may include difficulties in focusing, concentrating and/or with memory[9], and may partly explain lower functioning of patients with BD, even during euthymic periods[114].

Unfortunately, data are very limited with respect to treatment responses in patients with comorbid ADHD and BD, particularly in adults. Post and Kurlansik[115] asserted, without providing a reason, that stimulants should be avoided in adult patients with comorbid ADHD and BD, in favor of mood stabilizers or atypical antipsychotics. This may be due to the view outlined in reviews by Scheffer[11] and Klassen *et al.*[8] that stimulants may exacerbate manic symptoms in patients with comorbid ADHD-BD. Indeed, in a retrospective chart review, DelBello *et al.*[116] found that, for 21 adolescents with BD who had been exposed to stimulant therapy for a mean ± SD duration of 48 ± 35 months before the onset of BD, the mean ± SD age of BD onset (10.7 ± 3.9 years) was significantly lower ($p = 0.01$) than in 13 adolescents with BD who had not been treated with stimulants (13.9 ± 3.7 years). The mean ± SD age of onset of BD was also significantly lower ($p = 0.04$) when adolescent patients had been treated with at least two stimulants ($n = 9$, 8.9 ± 4.6 years) than those treated only with methylphenidate ($n = 9$, 12.7 ± 2.1 years)[116]. However, in 40 children/adolescents (6–17 years old) with comorbid ADHD-BD, it was reported that psychostimulants did not worsen symptoms of mania[32]. In these youngsters, ADHD was safely and effectively treated with psychostimulants (mixed amphetamine salts) after mania was stabilized with divalproex sodium (a mood stabilizer), while the latter medication alone was not an effective treatment for the symptoms of ADHD[32]. Indeed, when treating patients with comorbid ADHD-BD, Scheffer[11] points out that a staged approach, initially using a mood stabilizer, is required.

Similarly, atomoxetine has also been found to be effective as a treatment for ADHD symptoms in a case series of seven children and adolescents with comorbid ADHD-BD, and via a subsequent open-label study in 12 youngsters, when the patients were also receiving mood stabilizers or antipsychotics[117,118]. In these two studies no patients developed mania[117,118]. There have been some reports of mania in patients with ADHD receiving atomoxetine, particularly if the patients had a family history of mood disorders[119–122], although it was not stated whether any of these patients also had BD, and these publications were individual case reports or uncontrolled studies. While these small-scale studies suggest that atomoxetine and stimulants may be effective treatments in children with comorbid ADHD-BD, we are not aware of any comparable studies in adults with ADHD-BD. Thus we can only postulate that stimulants and atomoxetine, when used with due caution, may be effective and safe in these adult patients with ADHD-BD when they are also treated with mood stabilizers to protect against episodes of depression or mania. Based on the current level of information, we do not recommend treatment of comorbid ADHD-BD with ADHD medications in the absence of mood stabilizers. Another potential treatment option, albeit based on one open-label 6 week study of adults with ADHD and BD (36 patients), is bupropion, which was effective in treating ADHD without clinically significant activation of mania[123]; however, it is said that bupropion only has "mild to moderate effects on both depression and ADHD"[11]. Olanzapine is also an efficacious treatment for manic or mixed episodes of BD-I, approved for this purpose in adults and adolescents[124–128], although no data are available specifically for patients with comorbid ADHD-BD. Thus, further controlled trials of all these medications are warranted in adults with comorbid ADHD and BD.

With regard to the staged approach to treating comorbid ADHD and BD, Scheffer[11] outlines the following schedule. First, Scheffer[11] asserts that when there are clear diagnoses of comorbid ADHD and BD, "one should first treat the more serious condition, in this case BD"; a view that is shared by experts in the treatment of ADHD[5,51]. According to Scheffer[11], a mood stabilizer should be applied, and addition of lithium or quetiapine as a second mood stabilizer may also be helpful, to treat both depression and mania; lamotrigine is also an option as a mood stabilizer with antidepressant activity. The second stage, and the most common if someone has a true comorbidity between ADHD and BD, is the addition of a medication targeted at ADHD, if ADHD symptoms remain a source of impairment following mood stabilization. Whether or not this stage is needed will depend on the severity of ADHD and the impact that the ADHD symptoms have on individuals' function and quality of life. The additional medication would usually be a stimulant[11] or atomoxetine. As mentioned above, in children and adolescents with ADHD and BD, improvements in ADHD

symptoms may be gained, potentially without developing mania, using atomoxetine alongside mood stabilizers or antipsychotics[117,118]. In our experience and that of other experts in the treatment of ADHD[51], the risks of precipitating mania or depression with stimulant medications used alongside mood stabilizers is similarly low.

Alternatively, when a clear diagnosis of ADHD is made, and BD is only suspected and the patient does not meet the criteria for BD, then ADHD could be treated first[11]. However, due care must be taken to monitor potential worsening of BD symptoms in patients where BD is suspected since, as discussed above, either stimulants or atomoxetine might exacerbate subthreshold mania, particularly in the absence of a mood stabilizer. In our opinion and that of other experts[51], to avoid this situation it is always important to be as clear as possible about whether BD is present or not, and then treat the BD first if diagnosed. At the same time it is important to avoid the situation where someone with ADHD is treated ineffectively with mood stabilizers, a scenario that, in our experience, is not uncommon when patients are seen by an adult psychiatrist with limited experience of clinical management of ADHD. Most notably, ADHD in adults is usually accompanied by some degree of emotional instability and mood lability[38], which when severe and accompanied by hyperactivity and restlessness may look like a form of chronic hypomania. The important point here is that clinical trials with stimulants and atomoxetine show that improvements in symptoms of emotional dysregulation in adult patients with ADHD have a similar effect size to that seen for the core symptoms of ADHD[129–131]. Indeed, in one study, strong covariation during the treatment response was reported between the symptoms of emotional dysregulation and inattention and hyperactivity/impulsivity[129].

Conversely, if a patient's BD is mistaken for ADHD with emotional lability, and thus the BD is left untreated, this can have severe consequences. In the few rare cases where BD emerges during treatment of ADHD, the recommendation is to stop the ADHD treatment until BD has stabilized and then review the diagnosis of ADHD before considering further treatment. If stimulants are used in patients with BD, patients should be frequently assessed for possible symptoms of mania, as these symptoms may occur acutely or after several months of effective treatment of ADHD[11]. If mania symptoms arise, discontinue the stimulant and use a mood stabilizer (antimanic agent)[11]. Currently we are not aware of any evidence that supports the use of mood stabilizers or antipsychotics as an effective way to control the emotional lability that is commonly seen in ADHD.

Current evidence indicates that long-term psychotherapy is the primary treatment for BPD[132]. Data are very limited in relation to the treatment of comorbid BPD and ADHD. However, Philipsen[14] has described a structured skills training program tailored for adults with ADHD, based on the principles of dialectical behavioral treatment (DBT) for BPD, developed by Linehan[44]. In two open-label studies of this treatment, patients with ADHD showed statistically significant ($p<0.05$) improvements on all psychometric scales[40,133]. For instance, in 72 adults with ADHD, the ADHD Checklist (ADHD-CL) scores decreased from 23.3 to 19.3, 16 item Symptom Checklist-90-R (SCL-90-R) scores decreased from 24.7 to 19.9, Beck Depression Inventory (BDI) scores decreased from 16.2 to 11.3, and visual analogue scale (VAS) scores, used to measure overall personal health (0 = worst, 9 = best), increased from 3.6 to 5.7[133]. Other cognitive behavioral approaches for adults with ADHD have also been reported, including cognitive behavioral psychotherapy (CBT) combined with psychopharmacological treatment which was associated with better outcomes than psychopharmacology alone[134].

According to an extensive review by Stoffers *et al.*[135], while many patients with BPD receive 'off label' medications, no robust evidence of efficacy exists for pharmacotherapies in relation to "the core BPD symptoms of chronic feelings of emptiness, identity disturbance and abandonment". Indeed, these three symptoms did not improve in placebo-controlled studies of 'off label' olanzapine (which may antagonize serotonin and dopamine receptors) or quetiapine (a dopamine, serotonin, and adrenergic antagonist)[136,137]. However, some medications may be effective treatments for individual symptoms of BPD or symptoms of comorbid conditions[14]. ADHD and BPD are both characterized by impulsivity; this behavior may involve the serotonergic[138] and noradrenergic systems[139]. Some medications that affect these systems, such as selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics, have, in a few studies, been shown to reduce impulsivity in patients with BPD[135,137,140,141], and serotonergic dysfunction has been reported in ADHD[142]. With regard to the noradrenergic systems, clonidine treatment, which has been reported to effectively reduce impulsivity and hyperactivity in children and adolescents with ADHD, may also reduce aversive inner tension and the urge to self-harm in patients with BPD[143]. With regard to methylphenidate, there appears to be very limited data in relation to treatment of patients with comorbid ADHD-BPD. A small-scale (14 patients) open-label study has been published, suggesting that methylphenidate may improve ADHD and BPD symptoms in adolescent girls with this comorbidity[144]. For another study of adolescent girls (12 patients) with ADHD and comorbid BPD, it was concluded that "methylphenidate may attenuate smoking behavior"[145].

However, to the best of our knowledge, the effects of potential treatments for ADHD and/or BPD have not been investigated in large-scale controlled trials specifically in adults with concomitant ADHD and BPD, and the outcomes in individual patients may not be very predictable.

In our clinical experience, if the core syndrome of ADHD improves then patients with comorbid personality disorders are likely to be less distressed, function better in their daily lives, and have more control over their behavior. Furthermore, they are more likely to engage with and benefit from psychological treatment programs for BPD. These patients are also likely to show less mood instability; however, this may depend on whether the mood instability is primarily linked to ADHD or the processes that lead to BPD. We are aware of some cases of comorbid ADHD-BPD for which dramatic improvements were seen due to treatment and control of ADHD symptoms, sometimes to the extent that these patients no long meet BPD criteria. However, in other patients no such improvements in BPD symptoms were seen. Based on our clinical experience, we are of the opinion that ADHD should always be treated in patients with a comorbid personality disorder, given the potential benefits. However, it is a matter of concern that the current literature does not provide an evidence base to properly evaluate this conclusion.

More generally, we occasionally see cases referred to ADHD specialist clinics where the primary diagnosis is severe combined type ADHD, but where the patients have been considered for many years to have a primary diagnosis of a personality disorder. This is not surprising given the similarities of early onset, chronic trait-like course, impulsivity, emotional instability and social, behavioral and functional impairments seen in patients with both disorders. Mistaking ADHD for a personality disorder will have severe long-term consequences for patients who would otherwise receive potentially effective treatments of their ADHD symptoms. It is therefore critical that clinicians working with personality disorder patients consider ADHD as a potential diagnosis or comorbidity and consider treatment in these cases.

Conclusion

As ADHD, BD and BPD have overlapping symptom profiles, these disorders can be difficult to differentiate and accurately diagnose, particularly as our current diagnostic framework is symptom-based rather than based on underlying etiology. Moreover, ADHD is frequently found concomitant with BD or BPD, thus further complicating identification of these conditions, and possibly causing patient functioning to be worse than in the presence of only one of these conditions, as shown for patients with comorbid ADHD-BD[23–25]. Hence, it is important to accurately diagnose and appropriately treat each disorder, whether comorbid or occurring in isolation, to achieve higher levels of patient functioning. Notably, differentiating between these diagnoses is usually possible by paying attention to the onset and course of the symptomatology and identifying the core symptom clusters that define each condition. While genetic and neurobiological investigations are ongoing to identify robust biomarkers for all three conditions, it is likely that clinical acumen will remain central to this process for many years to come. We therefore strongly urge that all mental health professionals gain training and experience in the diagnosis and clinical management of all three conditions. In our clinical experience, and as recommended by other ADHD experts[5,11,51], because BD is more severe than ADHD, BD should always be treated first in patients who also have ADHD. In relation to comorbid ADHD and BPD, dramatic improvements in functioning may be gained by treating ADHD first. Nevertheless, further studies are warranted to address the shortage of data in relation to treatment responses in adults with comorbid ADHD and BD or BPD.

Transparency

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Declaration of financial/other relationships

P.A. has disclosed that he has acted as a consultant on behalf of King's College London for Lilly, Shire, Janssen-Cilag, and Novartis. He has also received educational or research grants from Shire, Janssen-Cilag, Lilly, Vifor Pharma, and QBTech, and participated in educational meetings or talks, sponsored by the same companies. W.D. and V.P. have disclosed that they are full time employees and stockholders of Eli Lilly & Co. D.E.-H. has disclosed that she has acted as a consultant of Psychiatric University Hospital, Zürich, for Lilly, Novartis, and Janssen-Cilag, and participated in educational meetings or talks sponsored by the same companies, as well as by Shire. D.E.-H. has not received any educational or research grants from any company. P.M. has disclosed that he has received a grant from Guy's and St Thomas' Charity. A.H.Y. has disclosed that he has participated in paid lectures and advisory boards for all major pharmaceutical companies involved in affective disorders including Eli Lilly and has also received grant support from Eli Lilly and acted as an expert witness in legal proceedings.

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References

1. Turgay A, Goodman DW, Asherson P, et al. ADHD Transition Phase Model Working Group. Lifespan persistence of ADHD: the life transition model and its application. J Clin Psychiatry 2012;73:192-201

2. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol Med 2006;36:159-65
3. Lichtenstein P, Halldner L, Zetterqvist J, et al. Medication for attention deficit-hyperactivity disorder and criminality. N Engl J Med 2012;367:2006-14
4. Asherson P, Akehurst R, Kooij JJ, et al. Under diagnosis of adult ADHD: cultural influences and societal burden. J Atten Disord 2012;16(5 Suppl):20-38S
5. Kooij SJ, Bejerot S, Blackwell A, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC Psychiatry 2010;10:67
6. Kooij JJ, Huss M, Asherson P, et al. Distinguishing comorbidity and successful management of adult ADHD. J Atten Disord 2012;16(5 Suppl):3-19S
7. Cox DJ, Madaan V, Cox BS. Adult attention-deficit/hyperactivity disorder and driving: why and how to manage it. Curr Psychiatry Rep 2011;13:345-50
8. Klassen LJ, Katzman MA, Chokka P. Adult ADHD and its comorbidities, with a focus on bipolar disorder. J Affect Disord 2010;124:1-8
9. Kent L, Craddock N. Is there a relationship between attention deficit hyperactivity disorder and bipolar disorder? J Affect Disord 2003;73:211-21
10. Wingo AP, Ghaemi, SN. A systematic review of rates and diagnostic validity of comorbid adult attention-deficit/hyperactivity disorder and bipolar disorder. J Clin Psychiatry 2007;68:1776-84
11. Scheffer RE. Concurrent ADHD and bipolar disorder. Curr Psychiatry Rep 2007;9:415-19
12. Skirrow C, Hosang GM, Farmer AE, Asherson P. An update on the debated association between ADHD and bipolar disorder across the lifespan. J Affect Disord 2012;141:143-59
13. Atmaca M, Ozler S, Topuz M, Goldstein S. Attention deficit hyperactivity disorder erroneously diagnosed and treated as bipolar disorder. J Atten Disord 2009;13:197-8
14. Philipsen A. Differential diagnosis and comorbidity of attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD) in adults. Eur Arch Psychiatry Clin Neurosci 2006;256(Suppl 1):i42-6
15. Philipsen A, Feige B, Hesslinger B, et al. Borderline typical symptoms in adult patients with attention deficit/hyperactivity disorder. Atten Deficit Hyperact Disord 2009;1:11-18
16. Stein MA. Medical mimics and differential diagnosis in adult ADHD. CNS Spectr 2008;13(10 Suppl 15):14-16
17. McIntyre RS, Kennedy SH, Soczynska JK, et al. Attention-deficit/hyperactivity disorder in adults with bipolar disorder or major depressive disorder: results from the international mood disorders collaborative project. Prim Care Companion J Clin Psychiatry 2010;12(3):pii: PCC.09m00861. doi: 10.4088/PCC.09m00861gry
18. Tamam L, Karakus G, Ozpoyraz N. Comorbidity of adult attention-deficit hyperactivity disorder and bipolar disorder: prevalence and clinical correlates. Eur Arch Psychiatry Clin Neurosci 2008;258:385-93
19. Philipsen A, Limberger MF, Lieb K, et al. Attention-deficit hyperactivity disorder as a potentially aggravating factor in borderline personality disorder. Br J Psychiatry 2008;192:118-23
20. Ferrer M, Andión O, Matalí J, et al. Comorbid attention-deficit/hyperactivity disorder in borderline patients defines an impulsive subtype of borderline personality disorder. J Pers Disord 2010;24:812-22
21. Youngstrom EA, Arnold LE, Frazier TW. Bipolar and ADHD comorbidity: both artifact and outgrowth of shared mechanisms. Clin Psychol 2010;17:350-9
22. Milberger S, Biederman J, Faraone SV, et al. Attention deficit hyperactivity disorder and comorbid disorders: issues of overlapping symptoms. Am J Psychiatry 1995;152:1793-9
23. Bernardi S, Cortese S, Solanto M, et al. Bipolar disorder and comorbid attention deficit hyperactivity disorder. A distinct clinical phenotype? Clinical characteristics and temperamental traits. World J Biol Psychiatry 2010;11:656-66
24. Karaahmet E, Konuk N, Dalkilic A, et al. The comorbidity of adult attention-deficit/hyperactivity disorder in bipolar disorder patients. Compr Psychiatry 2013;54:549-55
25. Wilens TE, Biederman J, Wozniak J, et al. Can adults with attention-deficit/hyperactivity disorder be distinguished from those with comorbid bipolar disorder? Findings from a sample of clinically referred adults. Biol Psychiatry 2003;54:1-8
26. Nutt DJ, Fone K, Asherson P, et al. Evidence-based guidelines for management of attention-deficit/hyperactivity disorder in adolescents in transition to adult services and in adults: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2007;21:10-41
27. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA: American Psychiatric Publishing, 2013
28. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Arlington, VA: American Psychiatric Publishing, 2000
29. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry 2000;157:816-18
30. Larsson H, Dilshad R, Lichtenstein P, et al. Developmental trajectories of DSM-IV symptoms of attention-deficit/hyperactivity disorder: genetic effects, family risk and associated psychopathology. J Child Psychol Psychiatry 2011;52:954-63
31. Ronald A, Simonoff E, Kuntsi J, et al. Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. J Child Psychol Psychiatry 2008;49:535-42
32. Scheffer RE, Kowatch RA, Carmody T, et al. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. Am J Psychiatry 2005;162:58-64
33. Torralva T, Gleichgerrcht E, Torrente F, et al. Neuropsychological functioning in adult bipolar disorder and ADHD patients: a comparative study. Psychiatry Res 2011;186:261-6
34. Nierenberg AA, Miyahara S, Spencer T, et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. Biol Psychiatry 2005;57:1467-73
35. Van Schalkwyk GI, Schronen J. Attention-deficit hyperactivity disorder in adults: a guide for the general practitioner. S Afr Fam Pract 2011;53:131-4
36. Asherson P. Clinical assessment and treatment of attention deficit hyperactivity disorder in adults. Expert Rev Neurother 2005;5:525-39
37. Skirrow C, McLoughlin G, Kuntsi J, et al. Behavioral, neurocognitive and treatment overlap between attention-deficit/hyperactivity disorder and mood instability. Expert Rev Neurother 2009;9:489-503
38. Skirrow C, Asherson P. Emotional lability, comorbidity and impairment in adults with attention-deficit hyperactivity disorder. J Affect Disord 2013;147:80-6
39. Dowson J, Bazanis E, Rogers R, et al. Impulsivity in patients with borderline personality disorder. Compr Psychiatry 2004;45:29-36
40. Hesslinger B, Tebartz van Elst L, Nyberg E, et al. Psychotherapy of attention deficit hyperactivity disorder in adults – a pilot study using a structured skills training program. Eur Arch Psychiatry Clin Neurosci 2002;252:177-84
41. Barnow S, Rüge J, Spitzer C, et al. [Temperament and character in persons with borderline personality disorder]. Nervenarzt 2005;76:839-48
42. Fossati A, Donati D, Donini M, et al. Temperament, character, and attachment patterns in borderline personality disorder. J Pers Disord 2001;15:390-402
43. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 2007;64:543-52
44. Linehan MM. Cognitive–behavioral treatment of borderline personality disorder. New York: Guilford Press, 1993
45. Miller CJ, Flory JD, Miller SR, et al. Childhood attention-deficit/hyperactivity disorder and the emergence of personality disorders in adolescence: a prospective follow-up study. J Clin Psychiatry 2008;69:1477-84
46. Distel MA, Carlier A, Middeldorp CM, et al. Borderline personality traits and adult attention-deficit hyperactivity disorder symptoms: a genetic analysis of comorbidity. Am J Med Genet B Neuropsychiatr Genet 2011;156B:817-25
47. Culpepper L, Mattingly G. A practical guide to recognition and diagnosis of ADHD in adults in the primary care setting. Postgrad Med 2008;120:16-26

48. Kooij JJS. Adult ADHD: Diagnostic Assessment and Treatment. Amsterdam, The Netherlands: Pearson Assessment and Information, 2013
49. Ginsberg Y, Hirvikoski T, Lindefors N. Attention deficit hyperactivity disorder (ADHD) among longer-term prison inmates is a prevalent, persistent and disabling disorder. BMC Psychiatry 2010;10:112
50. Rao P, Place M. Prevalence of ADHD in four general adult outpatient clinics in North East England. Prog Neurol Psychiatry 2011;15:7-10
51. UKAAN. Handbook for Adult ADHD. London: Springer Healthcare, 2013
52. Barkley R, Murphy K. A Clinical Workbook: Attention-Deficit Hyperactivity Disorder. New York: Guilford Press, 1998
53. Van de Glind G, van den Brink W, Koeter MW, et al. Validity of the Adult ADHD Self-Report Scale (ASRS) as a screener for adult ADHD in treatment seeking substance use disorder patients. Drug Alcohol Depend 2013;132:587-96
54. Nielsen NP, Wiig EH. AQT cognitive speed and processing efficiency differentiate adults with and without ADHD: a preliminary study. Int J Psychiatry Clin Pract 2011;15:219-27
55. Söderström S, Pettersson R, Nilsson KW. Quantitative and subjective behavioural aspects in the assessment of attention-deficit hyperactivity disorder (ADHD) in adults. Nord J Psychiatry 2014;68:30–7
56. Reh V, Schmidt M, Lam L, et al. Behavioral assessment of core ADHD symptoms using the QbTest. J Atten Disord 2013: epub ahead of print. doi:10.1177/1087054712472981
57. Angst J, Adolfsson R, Benazzi F, et al. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. J Affect Disord 2005;88:217-33
58. Halmøy A, Halleland H, Dramsdahl M, et al. Bipolar symptoms in adult attention-deficit/hyperactivity disorder: a cross-sectional study of 510 clinically diagnosed patients and 417 population-based controls. J Clin Psychiatry 2010;71:48-57
59. Picardi A. Rating scales in bipolar disorder. Curr Opin Psychiatry 2009;22:42-9
60. Mould G, Asherson P, Kuntsi J. King's College London, UK. Unpublished data
61. Zanarini MC, Vujanovic AA, Parachini EA, et al. A screening measure for BPD: the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). J Pers Disord 2003;17:568-73
62. Houston JP, Kroenke K, Faries DE, et al. A provisional screening instrument for four common mental disorders in adult primary care patients. Psychosomatics 2011;52:48-55
63. Faries DE, Houston JP, Sulcs EM, et al. A cross-validation of the provisional diagnostic instrument (PDI-4). BMC Fam Pract 2012;13:104
64. Epstein J, Johnson D, Conners CK. Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID). NY, USA: Multi Health Systems Inc., 1999
65. Kooij JJS, Francken MH. Diagnostic Interview for ADHD in Adults (DIVA 2.0). Available at: http://www.divacenter.eu [Last accessed 3 September 2013]
66. Primich C, Iennaco J. Diagnosing adult attention-deficit hyperactivity disorder: the importance of establishing daily life contexts for symptoms and impairments. J Psychiatr Ment Health Nurs 2012;19:362-73
67. Attention Deficit Hyperactivity Disorder. Diagnosis and Management of ADHD in Children, Young People and Adults. National Institute for Health & Clinical Excellence (NICE). Available at: http://www.nice.org.uk/nicemedia/live/12061/42059/42059.pdf [Last accessed 27 November 2013]
68. Adler LA. Epidemiology, impairments, and differential diagnosis in adult ADHD: introduction. CNS Spectr 2008;13(8 Suppl 12):4-5
69. Hamilton A. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62
70. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429-35
71. Gunderson JG, Kolb JE, Austin V. The diagnostic interview for borderline patients. Am J Psychiatry 1981;138:896-903
72. First MB, Gibbon M, Spitzer RL, et al. The Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II). Washington: American Psychiatric Press, 1997
73. Loranger AW, Sartorius N, Janca A. Assessment and Diagnosis of Personality Disorders: The International Personality Disorder Examination (IPDE). New York: Cambridge University Press, 1996
74. Zanarini MC. Diagnostic Interview for Personality Disorders (DIPD). Belmont, MA: McLean Hospital, 1983
75. Pfohl B, Blum N, Zimmerman M. Structured Interview for DSM-IV personality (SIDP-IV). Washington DC: American Psychiatric Press, 1997
76. Zanarini MC, Vujanovic AA, Parachini EA, et al. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): a continuous measure of DSM-IV borderline psychopathology. J Pers Disord 2003;17:233-42
77. Moran P, Crawford MJ. Assessing the severity of borderline personality disorder. Br J Psychiatry 2013;203:163-4
78. Nylander L, Holmqvist M, Gustafson L, et al. ADHD in adult psychiatry. Minimum rates and clinical presentation in general psychiatry outpatients. Nord J Psychiatry 2009;63:64-71
79. Almeida Montes LG, Hernández García AO, Ricardo-Garcell J. ADHD prevalence in adult outpatients with nonpsychotic psychiatric illnesses. J Atten Disord 2007;11:150-6
80. Zimmerman M, Rothschild L, Chelminski I. The prevalence of DSM-IV personality disorders in psychiatric outpatients. Am J Psychiatry 2005;162:1911-18
81. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry 2006;163:716-23
82. Fayyad J, De Graaf R, Kessler R, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry 2007;190:402-9
83. Simon V, Czobor P, Bálint S, et al. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry 2009;194:204-11
84. Rucklidge JJ. Gender differences in attention-deficit/hyperactivity disorder. Psychiatr Clin North Am 2010;33:357-73
85. Larsson H, Asherson P, Chang Z, et al. Genetic and environmental influences on adult attention deficit hyperactivity disorder symptoms: a large Swedish population-based study of twins. Psychol Med 2013;43:197-207
86. Bitter I, Simon V, Bálint S, et al. How do different diagnostic criteria, age and gender affect the prevalence of attention deficit hyperactivity disorder in adults? An epidemiological study in a Hungarian community sample. Eur Arch Psychiatry Clin Neurosci 2010;260:287-96
87. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 2011;68:241-51
88. Ayuso-Mateos JL. Global burden of bipolar disorder in the year 2000. World Health Organization, 2006. Available at: http://www.who.int/healthinfo/statistics/bod_bipolar.pdf [Last accessed 6 September 2013]
89. Coid J, Yang M, Tyrer P, et al. Prevalence and correlates of personality disorder in Great Britain. Br J Psychiatry 2006;188:423-31
90. Samuels J, Eaton WW, Bienvenu OJ III, et al. Prevalence and correlates of personality disorders in a community sample. Br J Psychiatry 2002;180:536-42
91. Grant BF, Chou SP, Goldstein RB, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2008;69:533-45
92. Angst J, Azorin JM, Bowden CL, et al. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. Arch Gen Psychiatry 2011;68:791-8
93. Angst J, Gamma A, Bowden CL, et al. Evidence-based definitions of bipolar-I and bipolar-II disorders among 5635 patients with major depressive episodes in the Bridge Study: validity and comorbidity. Eur Arch Psychiatry Clin Neurosci 2013;263:663-73
94. Angst J, Cui L, Swendsen J, et al. Major depressive disorder with subthreshold bipolarity in the National Comorbidity Survey Replication. Am J Psychiatry 2010;167:1194-201
95. Masi G, Perugi G, Toni C, et al. Attention-deficit hyperactivity disorder – bipolar comorbidity in children and adolescents. Bipolar Disord 2006;8:373-81

96. Tamam L, Tuğlu C, Karatas G, et al. Adult attention-deficit hyperactivity disorder in patients with bipolar I disorder in remission: preliminary study. Psychiatry Clin Neurosci 2006;60:480-5
97. Rydén E, Thase ME, Stråht D, et al. A history of childhood attention-deficit hyperactivity disorder (ADHD) impacts clinical outcome in adult bipolar patients regardless of current ADHD. Acta Psychiatrica Scandinavica 2009;120:239-46
98. Sachs GS, Baldassano CF, Truman CJ, et al. Comorbidity of attention deficit hyperactivity disorder with early- and late-onset bipolar disorder. Am J Psychiatry 2000;157:466-8
99. Larsson H, Rydén E, Boman M, et al. Risk of bipolar disorder and schizophrenia in relatives of people with attention-deficit hyperactivity disorder. Br J Psychiatry 2013;203:103-6
100. Faraone SV, Biederman J, Mennin D, et al. Bipolar and antisocial disorders among relatives of ADHD children: parsing familial subtypes of illness. Am J Med Genet 1998;81:108-16
101. Faraone SV, Biederman J, Monuteaux MC. Attention deficit hyperactivity disorder with bipolar disorder in girls: further evidence for a familial subtype? J Affect Disord 2001;64:19-26
102. Biederman J, Makris N, Valera EM, et al. Towards further understanding of the co-morbidity between attention deficit hyperactivity disorder and bipolar disorder: a MRI study of brain volumes. Psychol Med 2008;38:1045-56
103. Monuteaux MC, Seidman LJ, Faraone SV, et al. A preliminary study of dopamine D4 receptor genotype and structural brain alterations in adults with ADHD. Am J Med Genet B Neuropsychiatr Genet 2008;147B:1436-41
104. Brown A, Biederman J, Valera E, et al. Working memory network alterations and associated symptoms in adults with ADHD and bipolar disorder. J Psychiatric Res 2012;46:476-83
105. Makris N, Seidman LJ, Brown A, et al. Further understanding of the comorbidity between attention-deficit/hyperactivity disorder and bipolar disorder in adults: an MRI study of cortical thickness. Psychiatry Res 2012;202:1-11
106. Cumyn L, French L, Hechtman L. Comorbidity in adults with attention-deficit hyperactivity disorder. Can J Psychiatry 2009;54:673-83
107. Sobanski E, Banaschewski T, Asherson P, et al. Emotional lability in children and adolescents with attention deficit/hyperactivity disorder (ADHD): clinical correlates and familial prevalence. J Child Psychol Psychiatry 2010;51:915-23
108. Merwood A. Exploring the aetiology of ADHD: rater effects, the comorbidity with temperament and emotional lability, and polygenic scores. [PhD thesis]. King's College London, 2013
109. Hesslinger B, Tebartz van Elst L, Thiel T, et al. Frontoorbital volume reductions in adult patients with attention deficit hyperactivity disorder. Neurosci Lett 2002;328:319-21
110. Ernst M, Kimes AS, London ED, et al. Neural substrates of decision making in adults with attention deficit hyperactivity disorder. Am J Psychiatry 2003;160:1061-70
111. Schmahl CG, Vermetten E, Elzinga BM, et al. A positron emission tomography study of memories of childhood abuse in borderline personality disorder. Biol Psychiatry 2004;55:759-65
112. Soloff PH, Meltzer CC, Greer PJ, et al. Fenfluramine-activated FDG-PET study of borderline personality disorder. Biol Psychiatry 2000;47:540-7
113. Vollm B, Richardson P, Stirling J, et al. Neurobiological substrates of antisocial and borderline personality disorder: preliminary results of a functional FMRI study. Crim Behav Ment Health 2004;14:39-54
114. Malhi GS, Ivanovski B, Hadzi-Pavlovic D, et al. Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. Bipolar Disord 2007;9:114-25
115. Post RE, Kurlansik SL. Diagnosis and management of adult attention-deficit/hyperactivity disorder. Am Fam Physician 2012;85:890-6
116. DelBello MP, Soutullo CA, Hendricks W, et al. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. Bipolar Disord 2001;3:53-7
117. Chang K, Nayar D, Howe M, Rana M. Atomoxetine as an adjunct therapy in the treatment of co-morbid attention-deficit/hyperactivity disorder in children and adolescents with bipolar I or II disorder. J Child Adolesc Psychopharmacol 2009;19:547-51
118. Bahali K, Uneri OS, Ipek H. Atomoxetine-induced mania-like symptoms in an adolescent patient. Actas Esp Psiquiatr 2013;41:137-8
119. Hah M, Chang K. Atomoxetine for the treatment of attention-deficit/hyperactivity disorder in children and adolescents with bipolar disorders. J Child Adolesc Psychopharmacol 2005;15:996-1004
120. Henderson TA. Mania induction associated with atomoxetine. J Clin Psychopharmacol 2004;24:567-8
121. Henderson TA, Hartman K. Aggression, mania, and hypomania induction associated with atomoxetine. Pediatrics 2004;114:895-6
122. Steinberg S, Chouinard G. A case of mania associated with tomoxetine. Am J Psychiatry 1985;142:1517-18
123. Wilens TE, Prince JB, Spencer T, et al. An open trial of bupropion for the treatment of adults with attention-deficit/hyperactivity disorder and bipolar disorder. Biol Psychiatry 2003;54:9-16
124. Katagiri H, Tohen M, McDonnell DP, et al. Efficacy and safety of olanzapine for treatment of patients with bipolar depression: Japanese subpopulation analysis of a randomized, double-blind, placebo-controlled study. BMC Psychiatry 2013;13:138
125. Gonzalez-Pinto A, Vieta E, Reed C. Effectiveness of olanzapine monotherapy and olanzapine combination treatment in the long term following acute mania – results of a two year observational study in bipolar disorder (EMBLEM). J Affect Disord 2011;131:320-9
126. Bobo WV, Epstein RA, Shelton RC. Olanzapine monotherapy for acute depression in patients with bipolar I or II disorder: results of an 8-week open label trial. Hum Psychopharmacol 2010;25:30-6
127. Tohen M, Calabrese JR, Sachs GS, et al. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. Am J Psychiatry 2006;163:247-56
128. Olanzapine Prescribing Information. Eli Lilly and Company. Available at: http://pi.lilly.com/us/zyprexa-pi.pdf [Last accessed 12 November 2013]
129. Reimherr FW, Marchant BK, Strong RE, et al. Emotional dysregulation in adult ADHD and response to atomoxetine. Biol Psychiatry 2005;58:125-31
130. Reimherr FW, Williams ED, Strong RE, et al. A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. J Clin Psychiatry 2007;68:93-101
131. Rösler M, Retz W, Fischer R, et al. Twenty-four-week treatment with extended release methylphenidate improves emotional symptoms in adult ADHD. World J Biol Psychiatry 2002;11:709-18
132. Borderline Personality Disorder. The NICE Guidelines on Treatment and Management. National Institute for Health & Clinical Excellence (NICE). Available at: http://www.nice.org.uk/nicemedia/pdf/Borderline%20personality%20disorder%20full%20guideline-published.pdf [Last accessed 21 November 2013]
133. Philipsen A, Richter H, Peters J, et al. Structured group psychotherapy in adults with attention deficit hyperactivity disorder: results of an open multicentre study. J Nerv Ment Dis 2007;195:1013-19
134. Safren SA, Otto MW, Sprich S, et al. Cognitive–behavioral therapy for ADHD in medication treated adults with continued symptoms. Behav Res Ther 2005;43:831-42
135. Stoffers J, Völlm BA, Rücker G, et al. Pharmacological interventions for borderline personality disorder. Cochrane Database Syst Rev 2010;16:CD005653
136. Zanarini MC, Schulz SC, Detke HC, et al. A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2011;72:1353-62
137. Van den Eynde F, De Saedeleer S, Naudts K, et al. Quetiapine treatment and improved cognitive functioning in borderline personality disorder. Hum Psychopharmacol 2009;24:646-9
138. Dalley JW, Roiser JP. Dopamine, serotonin and impulsivity. Neuroscience 2012;215:42-58

139. Coccaro EF, Lee R, McCloskey M. Norepinephrine function in personality disorder: Plasma free MHPG correlates inversely with life history of aggression. CNS Spectr 2003;8:731-6
140. Rinne T, van den Brink W, Wouters L, et al. SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. Am J Psychiatry 2002;159:2048-54
141. Zanarini MC, Frankenburg FR, Parachini EAA. Preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine–fluoxetine combination in women with borderline personality disorder. J Clin Psychiatry 2004;65:903-7
142. Retz W, Freitag CM, Retz-Junginger P, et al. A functional serotonin transporter promoter gene polymorphism increases ADHD symptoms in delinquents: interaction with adverse childhood environment. Psychiatry Res 2008;158:123-31
143. Philipsen A, Richter H, Schmahl C, et al. Clonidine in acute aversive inner tension and self-injurious behavior in female patients with borderline personality disorder. J Clin Psychiatry 2004;65:1414-19
144. Golubchik P, Sever J, Zalsman G, et al. Methylphenidate in the treatment of female adolescents with cooccurrence of attention deficit/hyperactivity disorder and borderline personality disorder: a preliminary open-label trial. Int Clin Psychopharmacol 2008;23:228-31
145. Golubchik P, Sever J, Weizman A. Influence of methylphenidate treatment on smoking behavior in adolescent girls with attention-deficit/hyperactivity and borderline personality disorders. Clin Neuropharmacol 2009;32:239-42